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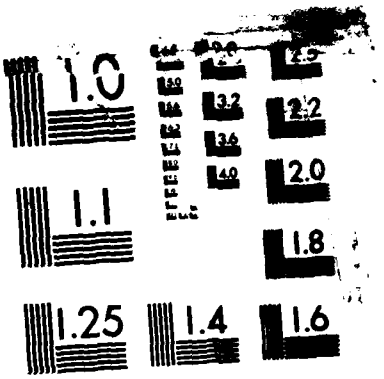

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EFFECTS OF HIGH ALTITUDE ON NEUROLOGICAL AND PULMONARY FUNCTION:
The Effect of High Altitude on Visual Evoked Potentials in Humans on Mt. Everest

FINAL REPORT

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Summary of Goals and Accomplishments of the Ultima Thule Everest Expedition. The goal of the Ultima Thule Everest Expedition was to investigate the effects of high altitude on cerebral function. We were interested in noninvasive methods of the assessment of cerebral function at altitude and thus used electrophysiological tests involving cortical evoked potential studies and a drug study using Dilantin and placebo in a double blind randomized fashion. The subjects were climbers and support members of the expedition. Our hypothesis was that acute mountain sickness was a form of cerebral edema and could be objectively assessed with visual evoked potential measurements. Visual evoked potentials were chosen since it has been shown that these wave forms are directly altered by raised intracranial pressure. Dilantin was chosen as a drug that works in the CNS and stabilizes brain function. We hypothesized that Dilantin might prevent some of the symptoms of acute mountain sickness. ---

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Our studies revealed that exposure to high altitude, both with and without the symptoms of acute mountain sickness, altered the evoked potential patterns in a significant fashion. With comparison of baseline measurements to high altitude measurements it was seen that certain individuals had objective evidence of transient raised intracranial pressure. The Dilantin study was minimally conclusive based on lack of symptoms of altitude sickness, thus making comparison of the effects of Dilantin to placebo very difficult. However, it was seen that the subjects taking Dilantin had fewer and less severe headaches than the placebo group.

It is apparent from our hypotheses and subsequent experimentation that these issues and results offer fertile ground for future studies.

FOREWARD

Citation of commercial organizations and trade names in this report does not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

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INTRODUCTION

Sojourners from sea level to high elevation often suffer from a variety of ailments. These include high altitude pulmonary edema, high altitude cerebral edema (HACE), and a symptom-complex including headache, letnargy, and nausea known as acute mountain sickness (AMS) (1). It is postulated that AMS is a group of symptoms caused by an acute increase in intracranial pressure (2,3). Changes in cortical visual evoked potentials (VEPs) have been shown to correlate with changes in intracranial pressures in humans (4,5).

To determine if VEPs might reflect changes in intracranial pressures during a prolonged high altitude excursion, VEPs were recorded serially on healthy male subjects (members of the Ultima Thule Everest Expedition) during an attempted climb to the summit of Mt. Everest. Along with these VEPs, a record of symptoms relating to AMS was maintained by all of the expedition members to determine if changes in VEPs might reflect the appearance and disappearance of AMS symptoms.

METHODS

Recordings of VEPs, oxygen saturation, and symptoms were recorded in standardized fashion on 16 male members of the Ultima Thule Everest Expedition, ages 25 to 46. The study protocol was designed to fit within the framework of the expedition. The technical and logistical problems of the harsh, remote environment are dealt with in a previous article (6).

Baseline VEPs were recorded at sea level in Seattle using a modified Nicolet CA-1000 computer of averaged transients. The CA-1000 was altered to utilize a specially-built Tektronics CRT which could operate under conditions of low atmospheric pressure. Standardized placement of scalp electrodes was ensured by using an Electrocap (Bio-Systems, Inc.) with sites chosen at Cz (vertex), Oz (occiput), referenced to Fz. Impedance was always below 5 Kohms. A standardized pair of Nicolet 105A LED goggles was employed to deliver flashes monocularly at a rate of 2.1/second.

A 250 msec sample of brain activity was recorded following each stimulus, with a bandpass of 5.0 to 100 Hz, and was averaged across 100 repetitions. The CA-1000 filter rejected trials with excess noise. A second average of 100 trials was then recorded and the two superimposed averaged waveforms were plotted on an X-Y plotter. Latencies (msec) of major components of the VEP waveform were recorded on the hardcopy printout at this time. After recording from one eye, the same procedure was repeated on the other eye. Subjects were allowed to relax for about 10 minutes prior to recording, and were instructed to keep their eyelids loosely closed.

Recordings were made in a similar manner and using the same equipment at two altitudes during the Mt. Everest climb. At 17,000 feet elevation, measurements were taken from day 3 through day 18. Then, at 21,000 feet, recordings were made from day 41 through day 70, which was the end of the climb. Subjects were tested in the afternoon, at a time when the shelter interior was warmed to a comfortable temperature.

At the time of the VEP recordings, oxygen saturations were also measured with a Hewlett-Packard ear oximeter. Symptoms were logged by each individual on a daily basis, and were also noted by the experimenter at the time of the VEP recordings.

RESULTS

OXYGEN SATURATION: Oxygen saturation values were determined throughout the course of the climb at the two elevations the VEPS were measured. The results are presented in Table 1. As has been the case on other high altitude expeditions, the oxygen saturation levels gradually increased during the expedition. The lowest values were obtained when the climbers were first establishing camp at 21,000' (days 41-45), but by the end of the expedition the values at 21,000' were nearly the same as those at the beginning of the expedition at 17,000' elevation.

VISUAL EVOKED POTENTIALS: Two unbiased researchers independently scored the latencies of peaks in the averaged waveforms of the VEPs. Four characteristic positive and four negative peaks were determined for each tracing. The early peaks were first identified, with the N1 peak latency in the range of 47 msec at sea level, followed by a small positive peak at around 57 msec. The subsequent larger peaks were then identified (see Figure 1). Each individual maintained a distinctive pattern throughout the entire study, although peak latencies varied. The values of the two replicated waveforms were averaged, and treated in subsequent statistical analyses as one value.

The means, standard deviations, and standard errors are presented in Table 2 and Figure 2. The number of recordings at sea level is relatively large, due to the multiple testing of subjects. There is also a variation in the number of readings during each time period due to the movement of climbers on the mountain. This was particularly true near the end of the study, since the recording equipment was situated far above base camp where only those fit and feeling well could be found. Only the six highest climbing members were available on day 70, the final test day before equipment was evacuated.

Several trends are suggested by examination of this data. First, a latency increase can be seen upon moving from sea level to 17,000' in most of the peaks, and becomes more obvious by the second time period (7-12 days). During the final period of measurement at 17,000' (17-18 days), there appears to be a shift in the latencies back towards sea level values (in 7 of 8 peaks). This pattern is not repeated by moving the recording equipment with the climbers to 21,000', nor do there appear to be any major changes in the latencies as time progresses at the higher elevation. The early peaks tend to slow, and the later ones actually decrease, but neither to any large degree.

For further resolution of these impressions, the data were more closely scrutinized with two-tailed Student's t-tests for matched pairs. The results are presented in Table 3. Clearly, there is a significant increase in latencies during all phases of the climb when sea level is used as a reference. There is a slightly larger number of significant latency shifts in the earlier, lower elevation portion of the the climb than at the higher, later portion. There do not seem to be nearly as many significant latency shifts when one portion of the climb is compared to another (as opposed to using sea level as a reference). However, there is a suggestion of a decrease towards sea level values when peak latencies at 17,000' (days 3-6 and 7-12) are compared to those recorded during early times at 21,000' (days 41-45).

With the exception of peaks N3 and P2, all of the peaks showed significant increases when sea level was used as a reference. When various

periods of the climb were compared to each other, significant latency shifts were grouped in peaks N2, N4, and P4. Of these three peaks, N2 has the smallest standard deviation.

ILLNESS: During the expedition there were four cases involving cerebral dysfunction. Two of these involved transient ischemic attacks, both with no residual. These both occurred on day 11 of the expedition. One 45 year old climber, after climbing from 17,000' to 19,500' experienced lack of feeling in his entire left arm. Gross motor function was intact, but fine control was missing. This resolved in several hours, and the climber returned to Base Camp at 17,000' the next morning. His VEPs were within the normal range at that time. The other climber, climbing for the first time above 20,000' experienced transient scotomata and blurred vision. On return to Base Camp the next day, he too had normal VEPs.

The other two cases involved AMS. In one case, within one day of arriving at Base Camp, a 30 year old climber experienced severe, unrelenting headache, lethargy, and general malaise without an elevated temperature. This cleared dramatically by day 3, soon after treatment with acetazolamide. The first VEP tracings were made on day 4, after the symptoms had cleared, and were entirely within the group norms for that time.

The second case of AMS, occurring after 7 days at 19,500', has previously been reported (7). Similar symptoms of headache, lethargy, and malaise were experienced; and again cleared within 12 hours after acetazolamide therapy. VEPs were obtained before, during, and after the AMS symptoms. The peak latency times of these recordings are presented in Table 4. With the exception of P1, all peak latencies were slowed by more than two standard deviations from the mean.

DISCUSSION

The opportunity to study healthy humans under extreme chronic hypoxic conditions is rare, and no where can better hypoxic conditions be found than during a climb up the world's highest mountain peak (8). The Ultima Thule Mt. Everest expedition was gracious enough to let us conduct an on-going measure of cerebral function during their attempt to reach the summit of Mt. Everest via the northeast ridge in the spring of 1984. VEP recordings were started within four days of arrival at the 17,000' Base Camp. After one month, the equipment was moved to Camp 3 at 21,000', and remained there until after the final summit attempt, which reached to within 800' of the summit.

Other studies focusing on cerebral function have been made during exposure to high altitudes, and include measurement of cerebral blood flow (9), performance on batteries of psychological tests (10,11) and electroencephalographic recordings at high altitude (12). Forster and colleagues (13) reported measuring VEPs on seven subjects during a 12 day exposure to a 4300 m altitude. Apparently no low level baseline recordings were made. Although two instances of increased amplitude were noted during the first five days, followed by some amplitude reduction, no changes in VEP peak latencies were noted.

In our study, under much more extreme conditions, shifts in latency were noted, both from the sea level baseline and within the climb itself. Hypoxia can alter waveforms of cortical evoked potentials in animals (14-18), and in man (19). However, we do not feel that the changes in our VEPs

were due solely to hypoxic exposure. The pattern of oxygen saturation in our climbers corresponds to the previous finding that there is a gradual increase in saturation over time, at a given altitude. Indeed, the oxygen saturation levels in our climbers at 21,000' was nearly equal to the values at 17,000' during the beginning of the climb. These changes in oxygen saturation did not at all correlate with any changes in the VEPs. Oxygenation levels were lowest during the initial recordings at Camp 3, but the corresponding VEP latencies actually shortened towards the sea level baseline at that time. Furthermore, while oxygen levels continually improved during the remainder of the climb, there were no significant changes in the VEP latencies.

Prolongation of latencies of at least one wave of the VEP has been shown to correlate with the intracranial pressure changes in humans under certain clinical conditions. The N2 wave, which was felt to be the significant waveform in these previous studies, has the same latency (71 msec) as the sea level N2 (70.6 msec) in our study. Thus we feel that this is the same wave. Notably, this is the wave which shows the most significant number of changes over time in our study.

During the first 40 days of the expedition, the climbers were moving mostly between Base Camp and Camp 3. The VEP latencies during this time increased significantly, then seemed to again decrease towards the sea level baseline by the end of this first 41 day period. It was early in this initial period, when the latency slowing was most marked, that the two cases of AMS occurred. Although direct intracranial pressure measurements were not made, these findings are at least consistent with the hypothesis that intracranial pressure increases during sojourns to high altitude, and that further increases can result in AMS, at which time there is a generalized slowing of all the measured evoked potential waves. Thus, we feel that travel to high elevations presents another clinical setting in which the N2 wave can be used to follow the clinical condition of patients, and perhaps reflect changes in intracranial pressure.

Once the climbers were established at Camp 3 and above, there were no longer any further improvements in the VEPs, even though oxygen saturation level did increase. This fits well with the general observation that above a certain high elevation, there appears to no longer be adaptation, but instead a slow, generalized deterioration of physical condition. It should be noted that in our study, only those nine individuals who continued to perform well at the highest altitudes were able to continue to be included in the measurements near the end of the expedition. The inclusion of the others who had retired below Camp 3 could have caused a prolongation of the VEP latencies measured late in the expedition and, if anything, caused the values to reflect an even greater deterioration of VEP function.

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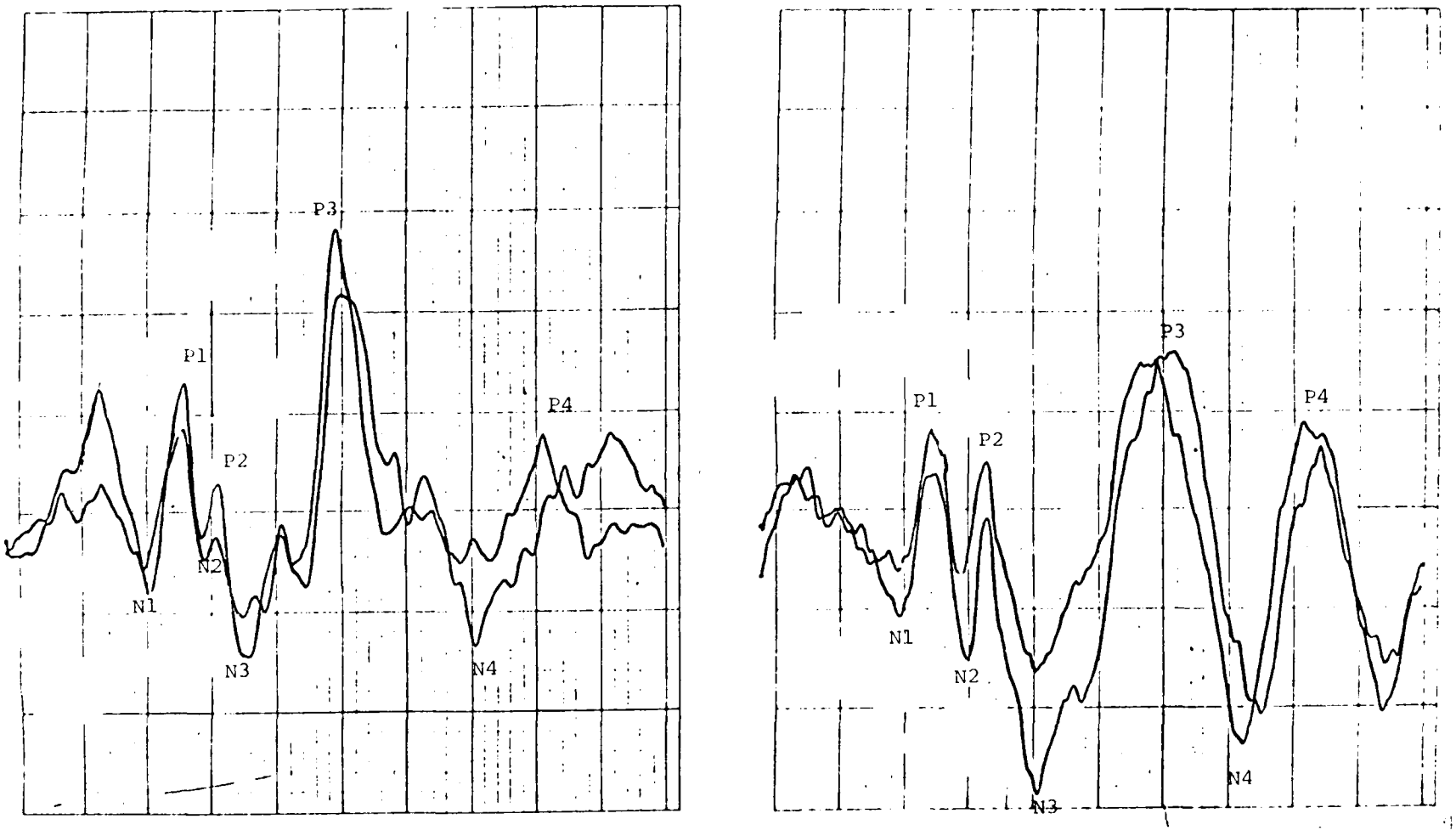
Figure 1



Representative EP Waveforms from Two Subjects at Sea Level

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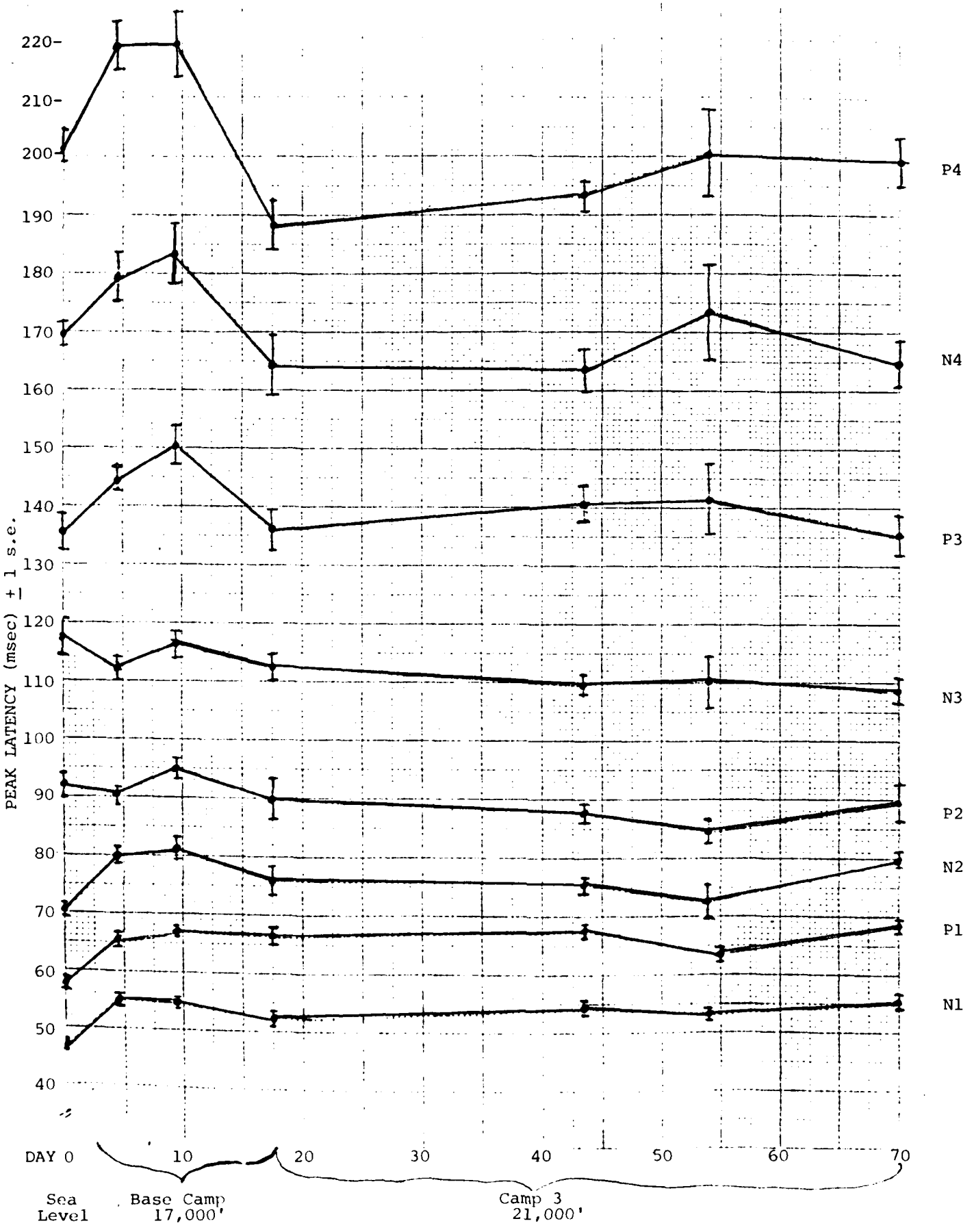

Figure 2

Means, and Standard Deviations of major peak latencies across days and locations

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Table 1

OXYGEN SATURATION LEVELS

Altitude	Time (Day #'s)	High Value	Low Value	Mean Value
17,000'	3-6	83	49	72.6
	7-12	82	64	73.2
	17-18	83	67	75.9
21,000'	41-45	72	45	67.4
	70	75	66	70.0

TABLE 2

PEAK LATENCIES ACROSS TIME PERIODS
(Means, Standard Deviations and Standard Errors)

Location	Day		N1	N2	N3	N4	P1	P2	P3	P4
Sea Level		Mean	46.94	70.63	117.53	169.10	57.70	92.00	135.37	201.76
		S.D.	4.80	6.57	21.28	18.70	3.61	14.08	22.02	18.35
		S.E.	0.72	0.99	3.17	2.78	0.54	2.09	3.28	2.76
17,000'	3-6	Mean	55.06	79.81	112.01	179.78	65.58	90.15	144.24	219.03
		S.D.	6.05	9.02	13.17	23.07	6.26	9.96	14.99	23.47
		S.E.	1.12	1.57	2.29	4.01	1.12	1.73	2.61	4.08
		N	29.00	33.00	33.00	33.00	31.00	33.00	33.00	33.00
	7-12	Mean	54.81	81.10	116.06	183.63	67.00	95.00	150.50	219.23
		S.D.	5.37	10.34	14.66	27.79	5.11	10.89	18.54	29.93
		S.E.	0.99	1.92	2.72	5.16	0.95	2.02	3.44	5.65
		N	29.00	29.00	29.00	29.00	29.00	29.00	29.00	28.00
	17-18	Mean	52.40	75.77	112.54	164.13	66.45	89.94	136.00	188.36
		S.D.	3.83	7.21	8.11	17.52	4.76	10.33	12.48	12.96
		S.E.	1.15	2.40	2.44	5.28	1.43	3.44	3.76	3.90
		N	11.00	9.00	11.00	11.00	11.00	9.00	11.00	11.00
21,000'	41-45	Mean	54.63	75.39	109.79	163.52	67.28	87.75	140.89	193.28
		S.D.	5.07	6.24	8.56	17.24	4.14	8.56	14.64	13.41
		S.E.	1.08	1.30	1.74	3.59	0.88	1.74	2.98	2.79
		N	22.00	23.00	24.00	23.00	22.00	24.00	24.00	23.00
	47-61	Mean	53.16	72.50	108.83	164.79	63.68	84.70	141.45	200.20
		S.D.	3.45	10.18	15.62	28.66	4.41	7.50	21.62	27.28
		S.E.	0.99	2.93	4.51	8.27	1.33	2.16	6.24	7.87
		N	12.00	12.00	12.00	12.00	11.00	12.00	12.00	12.00
	70	Mean	55.25	79.80	108.83	164.79	68.20	89.41	135.29	199.08
		S.D.	3.93	4.17	7.84	13.84	4.29	11.59	11.44	15.20
		S.E.	1.13	1.31	2.26	3.99	1.35	3.34	3.30	4.38
		N	10.00	12.00	12.00	12.00	12.00	10.00	12.00	12.00

TABLE 3

SIGNIFICANCE VALUES FOR PAIRED T-TESTS OF PEAK LATENCIES

Time #1	Time #2	N1	N2	N3	N4	P1	P2	P3	P4
0 Sea Level	3-6 17,000'	.001	.05	NS	.01	.001	NS	.025	.01
0 Sea Level	7-12 17,000'	.001	.01	NS	.05	.001	.05	.001	.05
0 Sea Level	17-18 17,000'	.001	.01	NS	NS	.001	.05	.01	.01
0 Sea Level	41-45 21,000'	.001	.001	NS	.01	.001	NS	.01	.01
0 Sea Level	47-61 21,000'	.025	NS	.05	.025	.05	NS	NS	NS
0 Sea Level	70 21,000'	.001	.01	NS	.001	.001	NS	NS	.01
3-6 17,000'	7-12 17,000'	NS	NS	NS	NS	NS	NS	NS	NS
3-6 17,000'	17-18 17,000'	NS	NS	NS	.025	NS	NS	NS	NS
3-6 17,000'	41-45 21,000'	NS	.01	NS	.001	NS	NS	NS	.001
3-6 17,000'	70 21,000'	NS	NS	NS	.05	NS	NS	NS	.001
7-12 17,000'	17-18 17,000'	.01	NS	NS	NS	NS	NS	NS	NS
7-12 17,000'	41-45 21,000'	NS	.01	NS	.025	NS	NS	.025	NS
41-45 21,000'	70 21,000'	NS	.001	NS	NS	NS	NS	.01	.025

TABLE 4

PEAK VALUES OF INDIVIDUAL CLIMBER'S EVOKED POTENTIALS
AVERAGED DURING CLIMB AND ON DAY OF AMS

	N1	N2	N3	N4	P1	P2	P3	P4
Mean (msec)	49.70	70.00	114.20	145.90	67.10	90.20	127.90	185.60
S.D.	3.37	2.04	12.01	10.60	6.35	2.73	13.20	8.20
AMS Day	63.80	84.50	153.00	188.50	71.80	116.80	159.80	227.80

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Phenytoin and Acute Mountain Sickness on Mount Everest

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Twenty-one climbers who were members of the American Ultima Thule Everest Expedition participated in a double-blind, randomized clinical trial of phenytoin prophylaxis for acute mountain sickness during the approach to the northeast ridge of Mount Everest. The study was carried out between Beijing and base camp at 16,800 feet. Time spent ascending from Beijing to base camp averaged 13 days. High-altitude symptom questionnaires were filled out beginning in Lhasa at 11,800 feet and in Xigatse at 12,000 feet, in Xegar at 14,000 feet, and at base camp. Computer analysis of the questionnaire answers performed by an impartial analyst revealed that climbers who took phenytoin were less likely to have headaches at base camp. No other statistically significant differences were observed, but the power of the sample size was low.

Two recent studies on the prevention of acute mountain sickness by acetazolamide [1] and dexamethasone [2] have concluded that both of these pharmaceutical agents are effective in the prevention of acute mountain sickness. However, both of these agents have unpleasant side effects. Acetazolamide can cause a tingling feeling in the extremities and in the perioral region, polyuria, and either lethargy or euphoria. It may also cause carbonated beverages, like beer, to have a metallic taste. The adverse effects of dexamethasone are potentially much more harmful and include peptic ulcer disease, activation of latent amebiasis or other infection, psychosis, salt retention, and masking of signs of infection. A prophylactic medication without such adverse effects would be desirable for the prevention of acute mountain sickness, since this disease occurs in persons who are in stressful circumstances at high altitude and who do not need the additional stress of adverse reactions to drugs. Such an alternative agent, phenytoin or diphenylhydantoin (Dilantin), was tested [3] and found to be ineffective at prevention of acute mountain sickness. However, the design of the experiment did not permit achievement of adequate serum level of the drug during the critical phase of exposure to high altitude. In addition, laboratory experimentation [4] has demonstrated that phenytoin can prevent pulmonary edema associated with cerebral hypoxia in dogs. Since this evidence was so striking, a clinical phenytoin study on the prevention of altitude sickness in human subjects was designed to assure that subjects received adequate doses of phenytoin prior to exposure to high altitude.

Since phenytoin is pharmacologically active in the brain, it was hypothesized that the drug may prevent acute mountain sickness, if acute mountain sickness is of neurogenic origin. The early signs and symptoms of acute mountain sickness may be related to early cerebral edema [5].

The approach to the north side of Mount Everest provided an ideal

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opportunity to study the effectiveness of phenytoin for prophylaxis of acute mountain sickness. Previous expeditions to this side of Mount Everest have noted a high rate of acute mountain sickness, high-altitude pulmonary edema, and high-altitude cerebral edema because of the rapid gain in altitude that is achieved through the use of airplanes, jeeps, and buses utilized to transport climbers through Tibet. The most prudent prophylaxis for acute mountain sickness is, of course, a slow ascent; however, this is extremely costly in terms of time and expense.

SUBJECTS AND METHODS

The study group consisted of 21 male climbers (aged 26 to 56) who normally reside at or near sea level. All were in excellent health and none ascended to altitudes over 14,500 feet for at least one month before participating in the study.

Fourteen subjects were climbing members of the Ultima Thule Expedition. Three subjects were trekkers who accompanied the expedition to their base camp. Four subjects were physicians who assisted with the climbing but were not slated for summit attempts.

The Expedition. The subjects arrived in Beijing, and after two to four days of sight-seeing, began their first day of study medications. The following day, the subjects flew to Chengdu in the Sechuan province of China. The following day, subjects were flown to Lhasa and remained there for three days. Ground transportation was then utilized to convey the subjects to base camp over a period of seven days for 18 subjects and three days for three subjects.

Study Design: Key Points. The research was designed to gradually allow phenytoin serum levels to build up without a loading dose, because of the possibility that a loading dose might cause the adverse reactions of nausea, nystagmus, lethargy, and ataxia, clearly undesirable in this particular subject population. Thus, the study was designed to show the maximal effects of phenytoin at the highest altitude obtained, i.e., after seven to 10 days of usage. Should there be any beneficial effects of this particular drug, they might only be seen at the end of the course of therapy.

Assessment of Acute Mountain Sickness. A modified general high-altitude questionnaire [6] was utilized to delineate and quantitate symptoms of acute mountain sickness. Twenty-two symptoms were listed as "yes"/"no" questions and rated on scales from 0, none; 1 to 3, slight; 4 to 6, moderate; and 7 to 9, extreme. Questionnaires were completed at Lhasa (11,800 feet), Xigatse (12,000 feet), Xegar (14,000 feet), and Everest base camp (16,800 feet). For purposes of statistical analysis, acute mountain sickness was defined as a headache of moderate or greater severity, nausea of slight or greater severity, or both. This is in keeping with the study performed by Larson et al [1].

RESULTS

The data were analyzed by an independent biostatistician data analyst. For almost all comparisons, a beneficial effect of phenytoin on symptoms of mountain sickness was not apparent except for the finding that few subjects who had headaches were in the phenytoin-treated group at the highest altitude.

TABLE I **Comparison of Phenytoin-Treated and Placebo-Treated Groups with Respect to History of Previous Altitude Sickness, Age, and Weight**

Previous altitude sickness* (no/yes)	
Placebo	3/9
Phenytoin	4/5
Age (years) (mean ± SD)	
Overall	38 ± 10.2
Placebo	40 ± 11.4
Phenytoin	35.5 ± 9.9
Weight (pounds) (mean ± SD)	
Overall	173.4 ± 20.9
Placebo	171 ± 28.8
Phenytoin	175.3 ± 14.5

* $\chi_1^2 = 0.875$.

Table I shows some basic checks of the randomization scheme. No significant differences between the phenytoin-treated and placebo-treated groups were noted with respect to history of previous altitude sickness, age, and weight.

Table II shows a comparison of environmental and other variables that are not associated with acute mountain sickness. There appeared to be no significant difference between the percent reporting sunburn or excessive coldness in the two groups at any altitude. Of interest, the placebo-treated group reported a more frequent need to urinate ($p < 0.05$).

Table III shows a preliminary analysis of headache and nausea. Although no individual variable yielded statistically significant differences by chi-square statistic, a distinctive trend was observed in the odds ratios as altitude increased, indicating that the phenytoin-treated group had fewer headaches. However, the mean severity among those answering "yes" to headaches was greater among the phenytoin-treated group at all altitudes. No difference was observed between the placebo-treated and phenytoin-treated groups for nausea, nor did there appear to be a trend over altitude. The group receiving phenytoin did seem to have more severe nausea among those answering "yes."

Table IV presents the results of a more extensive examination of the headache response using a log linear model. Analysis of variance supports the earlier observation indicating no difference in percent of headaches in the phenytoin-treated group but a trend ($p \approx$ approximately 0.10) of fewer headaches among the phenytoin-treated group as altitude increased.

Table V presents some basic descriptive statistics for three indexes: R (respiratory), C+, C− (cerebral). R is defined as the sum of the responses for "short of breath,"

TABLE II **Comparison of Environmental and Other Variables that Are Not Associated with Acute Mountain Sickness**

	12,000 Feet			12,500 Feet			14,050 Feet			16,700 Feet		
	No	Yes	Mean (yes)	No	Yes	Mean (yes)	No	Yes	Mean (yes)	No	Yes	Mean (yes)
Urinate												
Placebo	7	5	3.80	6	6	5.17	6	6	2.50	8	4	3.25
Phenytoin	7	2	4.50	7	2	6.00	8	1	4.00	9	0	0
Sunburn												
Placebo	8	3	1.66	10	2	1.50	11	1	2.00	11	1	2.00
Phenytoin	8	1	1.00	8	1	3.00	8	1	3.00	6	3	1.66
Cold												
Placebo	9	3	6.33	6	6	1.67	6	6	2.67	10	2	4.50
Phenytoin	7	2	4.00	6	3	3.50	6	3	4.00	6	3	3.33

TABLE III **Preliminary Analysis of Headache and Nausea**

	12,000 Feet			12,500 Feet			14,050 Feet			16,700 Feet		
	No	Yes	Mean (yes)	No	Yes	Mean (yes)	No	Yes	Mean (yes)	No	Yes	Mean (yes)
Headache												
Placebo	9	3	1.00	4	8	2.50	7	5	2.40	4	8	3.37
Phenytoin	6	3	3.33	3	6	5.00	7	2	5.50	6	3	4.30
Odds ratio		1.5			1			0.4			0.25	
Nausea												
Placebo	9	3	4.00	9	3	1.33	10	2	1.5	9	3	3.67
Phenytoin	8	1	6.00	7	2	6.5	9	0	0	8	1	5.00

TABLE IV **Results of an Analysis of Headache Using Log Linear Regression**

Source	ss	df	ms	F
Total	115.7	83		
Drug	1.0	1	1.0	0.59
Subject (drug)	32.0	19	1.68	
Altitude	0.4	1	0.4	0.35
Altitude × drug	3.6	1	3.6	3.2
Altitude × subject (drug)	Unavailable			
Error	68.7	61	1.12	

ss = sum of squares; df = degrees of freedom; ms = mean score; F = variance ratio.

TABLE V **Basic Descriptive Statistics for Three Indexes**

	12,000 Feet	12,500 Feet	14,050 Feet	16,700 Feet
R Index*				
Placebo	0.375	1.25	0.875	1.375
	1.125	1.44	0.96	2.04
	1.39	1.31	0.99	1.77
Phenytoin	0.25	1.0	2.00	1.25
	1.42	1.92	1.80	2.00
	1.68	1.71	1.71	2.16
C+ Index*				
Placebo	5.50	3.50	2.00	2.38
	4.29	3.75	2.64	2.91
	2.39	2.53	2.57	2.14
Phenytoin	3.00	2.50	1.75	2.50
	3.52	1.80	2.72	2.97
	2.70	1.81	2.40	2.61
C− Index*				
Placebo	0.83	0.75	0.58	1.25
	1.41	0.80	1.14	1.57
	1.75	0.85	1.32	1.47
Phenytoin	0.83	1.17	1.00	0.33
	1.07	1.30	1.50	1.42
	1.40	1.56	1.90	2.10

* See Results section for definition.

TABLE VI **Results of Analysis of Variance on R Index***

Source	ss	df	ms	F
Total	205.2	83		
Drug	3.2	1	3.2	0.5
Subject (drug)	122.2	19	6.4	
Altitude	4.7	1	4.7	2.97
Altitude × drug	0.4	1	0.4	0.25
Altitude × subject (drug)	30.0	19	1.58	
Error	44.6	42	1.06	

* See Results section for definition.
Abbreviations as in Table IV.

TABLE VII **Results of Analysis of Variance on C+ Index***

Source	ss	df	ms	F
Total	481.4	83		
Drug	8.9	1	3.9	0.54
Subject (drug)	308.3	19	16.2	
Altitude	6.0	1	6.0	2.73
Altitude × drug	7.0	1	7.0	3.18
Altitude × subject (drug)	41.8	19	2.2	
Error	109.4	42	2.6	

* See Results section for definition.
Abbreviations as in Table IV.

TABLE VIII **Results of Analysis of Variance on C− Index***

Source	ss	df	ms	F
Total	189.8	83		
Drug	0.3	1	0.3	0.059
Subject (drug)	97.3	19	5.1	
Altitude	1.3	1	1.3	0.68
Altitude × drug	0.03	1	0.03	0.01
Altitude × subject (drug)	36.45	19	1.92	
Error	54.42	42		

* See Results section for definition.
Abbreviations as in Table IV.

"tired," "lazy," and "heart pounding," divided by the number of responses for these items (typically four, but possibly less if there was no response to one of the questions). C+ is the average of "satisfied," "refreshed," "happy," and "vigorous." C− is the average of "dizzy," "drowsy," "tired," "lazy," "sleepy," and "trouble sleeping." In each case, a "no" was counted as 0. A "yes" with no score circled was treated the same as a nonresponse. Fortunately, this did not happen often.

Tables VI to **VIII** display results of analysis of variance on each index. In no cases were any effects of a drug effect observed.

The power of the study to detect meaningful differences due to drug effect was actually quite low. For example, at 12,000 feet, the probability of headache in the placebo-treated group was 0.25. With a $p = 0.05$ value, the one-sided probability of headache in the phenytoin-treated group would have to be 0.002 (essentially no headaches observed) to be debated 70 percent of the time. Stated another way, the power (beta) to detect a true change in the probability of headache from 0.25 to 0.15 was $\beta = 0.14$, which most would consider too low to confidently reject that phenytoin has no effect.

For continuous indexes (R, C+, and C−) in which the

variable averaged approximately 6.5, the power was similarly low: $\beta = 0.12$ to detect a difference of 0.25; $\beta = 0.18$ to detect a difference of 0.50.

COMMENTS

In this study, phenytoin appears to have ameliorated the frequency of headaches that occurred as climbers gained altitude up to 16,800 feet at the Everest base camp on the central Rongbuk glacier moraine. Headache, the principle manifestation of acute mountain sickness, is the symptom on which a drug effect might be expected to occur. Thus, the finding supports the hypothesis that phenytoin, presumably acting through its effect on the central nervous system, may alter the effect of hypoxia on the brain, thereby preventing or ameliorating acute mountain sickness at these altitudes. The findings must be viewed as preliminary, since the power of the study was extremely low and allowed us to detect rather large differences only in comparison with acetazolamide. However, the phenytoin drug effect seemed to be somewhat less, compared with the effects of acetazolamide. Direct comparisons should be viewed with caution given the different environments and ascent conditions. We are now sure that phenytoin has been, and is being, studied [7] on Mount Rainier, which may allow more meaningful comparisons. Of note, phenytoin was not associated with any side effects in this study.

Given the findings of the study, it would appear that further work is necessary to determine phenytoin's role in ameliorating acute mountain sickness. Such studies will need larger sample sizes and may be more powerful if rapid ascent and, therefore, increased roles of acute mountain sickness can be part of the protocol.

The following is an anecdotal additional observation. The study population was examined for retinal hemorrhages during the entire expedition. For the first six weeks of the trip, only one subject was noted to have retinal hemorrhages, although a number of subjects were noted to have retinal venous engorgement. This subject also experienced difficulties acclimatizing to each additional gain in altitude, beginning with the flight into Lhasa at 12,000 feet up until reaching his maximal point on the North Col head wall (22,500 feet). This person had been randomly assigned to the phenytoin-treated group. It is of interest that this one subject with retinal hemorrhages represented approximately 5 percent of the study population. This percentage is much less than that expected for a group attaining the altitude of 21,500 feet during the first six weeks of the expedition. It is unclear whether phenytoin played a role in the prevention of the expected higher incidence of retinal hemorrhages, and this represents a subject of possible future research.

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